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Unusual, selective, reductive, deoxygenation of cyclopentenone alcohols

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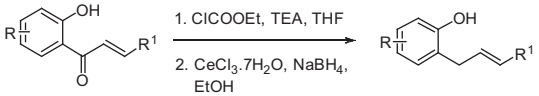
ABSTRACT

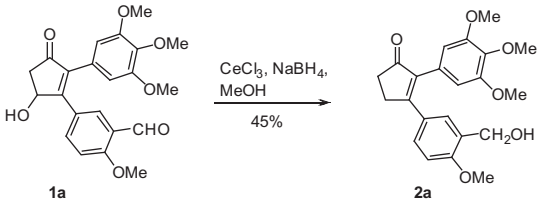
A selective, reductive, deoxygenation of 2-aryl-4-hydroxycyclopent-2-en-1-ones to afford 2-aryl-cyclopent-2-en-1-ones was achieved by $NaBH_4$–$CeCl_3$ in methanol.

Reduction of conjugated ketone functionality with sodium borohydride in methanol in the presence of rare earth halides to afford allylic alcohols was reported by Jean-Louis Luche in 1978.[1] Gemal and Luche further reported selective reduction of ketone in the presence of aldehyde using cerium chloride.[2] Various aspects of this reaction were studied extensively[3–12] by Luche and subsequently by many other chemists to explore the utility of this reaction. It has been found that during this reaction the carbonyl functionality is reduced to alcohol in a stereoselective manner making the method useful in the synthesis of optically active alcohols. This reaction has continued to attract synthetic chemists and recently it has been reported by Zhang and co-workers[13] that it can be utilized for deoxygenation of α,β-unsaturated acylphenols to obtain 2-allylphenols as depicted in Scheme 1. In the same publication, it has been reported that 2-acylphenols can also be converted to 2-ethylphenols using the same strategy.

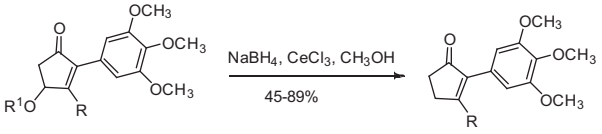
During the course of our research involving the Luche reduction of 2-aryl-4-hydroxycyclopent-2-en-1-ones, we found that selective deoxygenation takes place wherein protected/unprotected hydroxyl functionality is removed to afford the 2-aryl-cyclopent-2-en-1-ones and the results are reported herein. It is noteworthy that deoxygenation of hydroxyl functionality under Luche reduction conditions is not reported in the literature.



Scheme 1. Deoxygenation of 2-acylphenols (Ref. 13).



Scheme 2. Reduction of substituted cyclopentenone alcohol **1a**.



1a: R= 3-Formyl-4-methoxyphenyl, R^1= H
1b: R= 4-Methoxyphenyl, R^1= H
1c: R= 3-Acetyl-4-methoxyphenyl, R^1= H
1d: R= 4-Methoxyphenyl, R^1= TBDMS
1e: R=R^1=H
1f: R=H, R^1= TBDMS
1g: R=H, R^1= Ac
1h: R=H, R^1= Bz
1i: R=H, R^1= TBDPS

2a: R= 3-Hydroxymethyl-4-methoxyphenyl
2b: R= 4-Methoxyphenyl
2c: R= 3-(1-Hydroxyethyl)-4-methoxyphenyl
2d: R=H

Scheme 3. Selective, reductive deoxygenation of compounds **1**.

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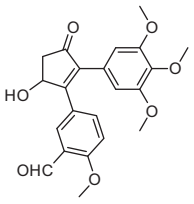
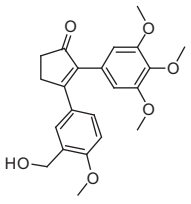
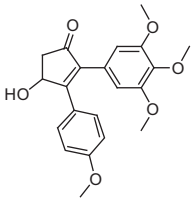
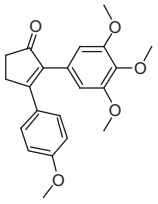
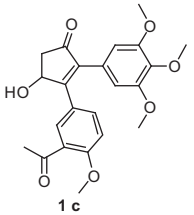
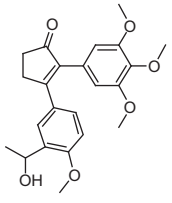
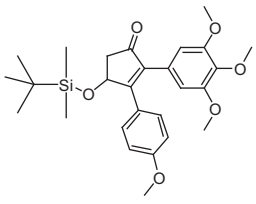
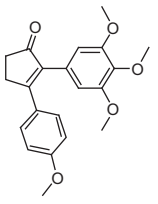
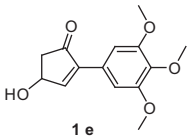
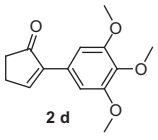
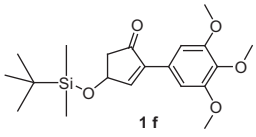
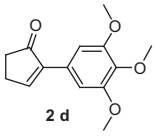
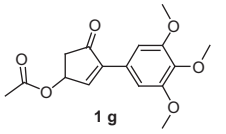
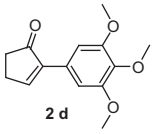
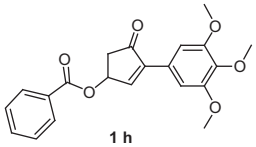
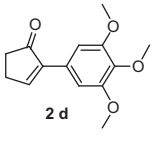
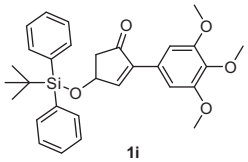
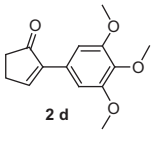
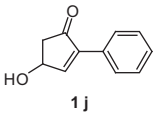
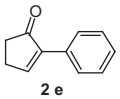
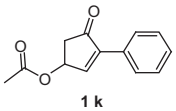
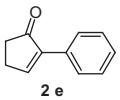
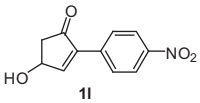
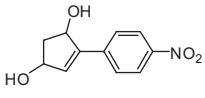
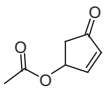
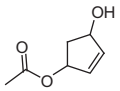
0040-4039/

Table 1
Selective reduction of compounds **1**

Entry	Reactant	Product	Yield[a] (%)
1	 1 a	 2 a	45
2	 1 b	 2 b	89
3	 1 c	 2 c	55
4	 1 d	 2 b	50
5	 1 e	 2 d	85
6	 1 f	 2 d	55
7	 1 g	 2 d	51
8	 1 h	 2 d	65
9	 1i	 2 d	49

[a] Isolated yield; variable amount of starting material was recovered.

Table 2
Selective reduction of compounds **1j–1m**

Entry	Reactant	Product	Yield[a] (%)
1	 1 j	 2 e	78
2	 1 k	 2 e	67
3	 1l	 2 f	43
4	 1 m	 2 g	75

[a] Isolated yield; variable amount of starting material was recovered.

Based on the reported information,[2] the substituted cyclopentenone alcohol **1a** was subjected to Luche reduction with an aim to obtain the corresponding diol. There was no reaction with one equivalent of sodium borohydride and cerium chloride so the reaction was attempted with varying amounts of sodium borohydride and cerium chloride. To our surprise, when the reaction was carried out with 2 equiv of cerium chloride and 3 equiv of sodium borohydride, the substituted cyclopentenone **2a** was obtained in 45% yield (Scheme 2) and rest of the starting material was recovered.

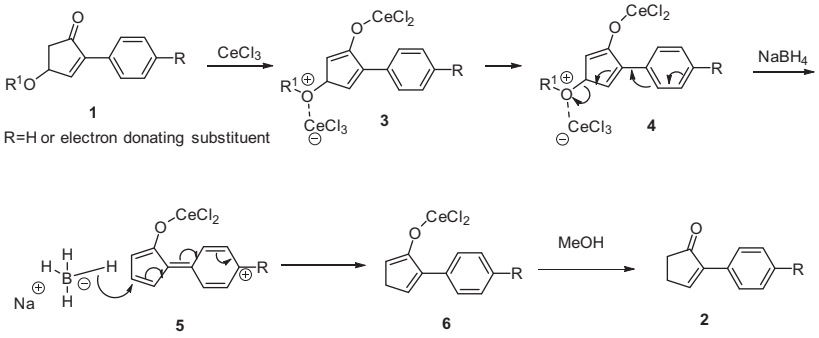
Thus, the ketone carbonyl in **1a** survived while the hydroxyl functionality was reductively removed and aldehyde was reduced to alcohol to afford the substituted cyclopentenone **2a**.

This unprecedented interesting result prompted us to check the generality of the reaction and a number of cyclopentenone alcohols were subjected to Luche reduction (Scheme 3).

It was observed that in all the above cases,[14,15] deoxygenation of cyclopentenone alcohols **1** took place to give cyclopentenones **2** in 2–3 h, instead of the reduction of ketone functionality, in good yields (Table 1).

The reaction was further studied for its scope and limitations. When 4-hydroxy-2-phenylcyclopent-2-en-1-one (**1j**) was subjected to similar reaction (Table 2, entry 1), 2-phenylcyclopent-2-en-1-one (**2e**) was obtained in 78% yield while the reaction of 4-acetoxy-2-phenylcyclopent-2-en-1-one (**1k**) afforded 2-phenylcyclopent-2-en-1-one (**2e**) in 67% yield (Table 2, entry 2). The reaction of 4-hydroxy-2-(4-nitrophenyl)cyclopent-2-en-1-one (**1l**) was slow and incomplete and resulted in the formation of 1,4-dihydroxy-2-(4-nitrophenyl)cyclopent-2-ene (**2f**) in 43% yield after 4 h. The corresponding 4-dehydroxylated product 2-(4-nitrophenyl) cyclopent-2-en-1-one was not obtained. Similarly, 4-acetoxycyclopent-2-en-1-one (**1m**) provided 1-acetoxy-4-hydroxycyclopent-2-ene (**2g**) in 75% yield and cyclopent-2-en-1-one was not obtained.

Thus, it was observed that the 4-(un)protectedhydroxycyclopent-2-en-1-ones bearing phenyl ring with electron donating substituent or unsubstituted phenyl ring, at 2-position of cyclopentenone undergo deoxygenation at 4-position while 4-(un)protectedhydroxycyclopent-2-en-1-ones bearing phenyl ring, with electron withdrawing substituent (e.g., nitro group), at 2-position of cyclopentenone undergo usual reduction of ketone functionality. In case of substrates with same substituents on aro-



Scheme 4. Proposed mechanism for deoxygenation.

matic ring, the substrates with 4-hydroxy groups give better yields than the substrates with 4-protected hydroxyl groups (e.g., **1b** gave 89% yield while **1d** gave 50% yield. Also, **1e** gave 85% yield while **1f**, **1g**, **1h**, and **1i** gave 55, 51, 65, and 49% yields respectively. Similarly, **1j** gave 78% yield whereas **1k** afforded 67% yield). 4-(un)Protectedhydroxycyclopent-2-en-1-ones (e.g., **1m**) without phenyl ring undergo normal reduction of ketone.

The proposed mechanism for this reaction is shown in Scheme 4.

In conclusion, the present manuscript reports interesting preliminary results about an unprecedented method for the selective one-step deoxygenation of 2-aryl-4-hydroxycyclopent-2-en-1-ones to afford 2-aryl-cyclopent-2-en-1-ones. The electron donating substituents on phenyl ring favor the deoxygenation while the electron withdrawing substituents favor the normal reduction of ketone to give corresponding hydroxy compounds.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.122.

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14. Spectral data for all products obtained are given in the Supplementary data.
15. *Representative experimental procedure:* Preparation of (3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)cyclopent-2-en-1-one: Compound **1b** (100 mg, 0.27 mmol) and $CeCl_3$ (132 mg, 0.54 mmol) in MeOH (10 ml) were stirred in a two-necked round bottom flask at 0 °C for 10 min. $NaBH_4$ (30 mg, 0.81 mmol) was added to it and the mixture was stirred and allowed to reach room temperature. Reaction was monitored by TLC (60% ethyl acetate in pet ether was used as a solvent system). After 2 h, water was added to it. Methanol in the reaction mixture was removed by using rotavapor and the product was extracted with ethyl acetate to obtain crude compound which was purified by using column chromatography to obtain pure compound **2b** (85 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67–2.72 (m, 2H), 3.03–3.08 (m, 2H), 3.75 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 6.44 (s, 2H), 6.82 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.07, 34.59, 55.31, 55.98 (2C), 60.83, 106.33 (2C), 113.74 (2C), 127.62, 128.43, 129.95 (2C), 137.50, 138.30, 153.43 (2C), 161.03, 167.27, 207.64; IR: 1698 cm^{-1}; HRMS (ESI) m/z calculated for [$C_{21}H_{22}O_5$+H]: 355.1540, found: 355.1541; [$C_{21}H_{22}O_5$+Na]: 377.1359, found: 377.1360.